REMARKS

Claim 1 has been amended by the addition of a substituent to the definition of R_1, as supported on page 1, 9th line containing words, page 2, lines 8-11, and original Claim 4, line 2; the deletion of one alternative definition for R_2; and stylistic changes, and previously-presented Claim 4 has been canceled.

Claim 5 has been amended consistent with an amendment to Claim 1 and the addition of minor grammatical and stylistic changes.

New Claim 12 is supported by Example 1, page 5, of the Specification.

No new matter has been added to the Application as a result of these amendments.

Claims 1-3, 5-8, and 10-12 are therefore now currently pending in the instant Application, for which a favorable reconsideration of this Application is respectfully requested.

Claims 1-8, 10 and 11 have been rejected under 35USC103(a) as unpatentable over Albert *et al* (WO 02/38561A1).

Published International Patent Application WO 02/38561A1 (Novartis AG, with Rainer Albert the first named inventor) describes: indolylmaleimide derivatives in free form or salt form, as optical isomers, racemates, or diastereoisomers, which compounds comprise a substituted phenyl, naphthyl, tetrahydronaphthyl, quinazolinyl, quinolyl, isoquinolyl or pyrimidinyl residue, and which compounds inhibit Protein Kinase C (PKC), T-cell activation and proliferation, and the proliferative response of T-cells to cytokines; processes for the preparation of these compounds; and pharmaceutical compositions comprising these compounds in free form or pharmaceutically-acceptable salt form with at least one pharmaceutically-acceptable carrier or diluent for, *inter*

alia, the treatment and/or prevention of T-cell-mediated acute or chronic inflammatory diseases or disorders, autoimmune diseases, graft rejection or cancer.

While there are some similarities between the '561 compounds and those of the instant invention, the reference does not describe or reasonably suggest the novel compounds of the instant invention. The '561 reference does not teach a pyridyl in the R-position- a clear omission among the six ring systems listed that would suggest to the skilled practitioner that the ring systems identified are of prime importance for the activity of their compounds, thus teaching away from substitution of pyridyl for phenyl or quinoline, as, otherwise, pyridine would certainly have been included with the ring systems identified in the reference.

Pyridine and phenyl are actually not even true bioisosteres, as they differ fundamentally in their electron distributions, i.e., phenyl is a truly aromatic moiety, following Hückel's (4n+2) Rule (for phenyl, n=1), but pyridine is not, as the two unpaired electrons from the nitrogen contribute to eight electrons, resulting in a different electron distribution, and thus, different sizes, polarities, etc., when comparing phenyl to pyridyl. Thus, a skilled routineer would not likely consider this substitution.

In addition, the exact position of the nitrogen in the pyridyl, between R_1 and the bond binding to the rest of the molecule, in Applicants' compounds from among the at least two other alternative positions is a distinguishing, and not insignificant, selection by Applicants. The significance of this selection is clearly demonstrated by the data from the CD28 costimulation assay (page 17 of the Specification) and the allogeneic mixed lymphocyte reaction assay (page 19 of the Specification) for Applicants' compound of Example 1 (and New Claim 12), which showed IC_{50} values of 13.0nM and 28.8nM, respectively, compared with the '561 compound having a comparable position of the nitrogen (Example 56, page 23- though a double ring and two ring nitrogens) that had values in the

same assays of only 42+/-12nM and 168+/-20nM, respectively (page 38, line 30 and page 39, line 14, respectively, of the '561 reference).

Finally, while Example 163 of the '561 reference may disclose piperazine in the R_{11}-position, the nitrogen in the quinolyl ring that correlates with Applicants' R is in a different position, and the second ring is not aromatic.

Thus, the '561 reference does not teach, and actually teaches away from use of a pyridyl in the R-position, and the importance of the position of the nitrogen, the ring chosen and the substitution with R_2, as shown above, which demonstrate a significant and unpredictable improvement, that is not suggested in the '561 reference, with Applicants' compounds over the prior art, clearly distinguish Applicants' invention over the '561 reference, suggesting that it is not merely the presence of the piperazine ring that is important, but the entire structure and components that makes the present compounds novel and unexpected.

Reconsideration and withdrawal of this rejection is, therefore, respectfully requested.

SUMMARY

In view of Applicants' amendments and arguments, they respectfully believe that all pending Claims are now in condition for allowance and earnestly solicit such favorable action, with an early Notice of Allowance being issued. If any remaining matters need to be resolved, however, Applicants respectfully request a telephone interview (the undersigned attorney may be contacted at the telephone number set forth below) with the Examiner prior to any adverse action being issued by the Office in response to these arguments, in order to facilitate allowance of the pending Claims.

Respectfully submitted,

Dated: February 11, 2009

By 
Richard A. Elder
Reg. No. 30,255

HOXIE & ASSOCIATES LLC
75 Main Street, Suite 301
Millburn, New Jersey 07041
(973) 912-5232